DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

October 4, 2002

By Certified Mail – Return Receipt Requested
and by Facsimile Transmission

CBER – 03 – 001

**Warning Letter**

Gary Frenette, M.D., Ph.D.
Blumenthal Cancer Center
Carolinas Medical Center
1000 Blythe Boulevard
Charlotte, North Carolina 28232

Dear Dr. Frenette:

During the inspection that ended on May 28, 2002, Tracy R. Ball, an investigator with the Food and Drug Administration (FDA), reviewed your conduct of a clinical study using the investigational product [redacted]. The sponsor, [redacted] has submitted data from this study to the FDA [redacted]. The inspection was conducted under the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of clinical research involving investigational drugs. At the close of the inspection, a Form FDA 483, List of Inspectional Observations, was issued to and discussed with you.

We have reviewed your letter to the FDA, dated July 11, 2002, in response to the Form FDA 483. We have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provision of the CFR is cited for each violation listed below.

**You failed to furnish accurate reports to the sponsor. [21 CFR § 312.64(a)].**

You failed to ensure the accuracy of data reported to the sponsor, which may compromise assessment of the safety and efficacy of the investigational product.

1. During the FDA inspection, your staff discovered that incorrect values for "actual administered doses" of the investigational product were entered on Case Report Forms (CRFs) for [redacted] of [redacted] subjects (Subjects [redacted]'). You submitted the CRFs containing the incorrect data to the sponsor.

Your staff provided a table of revised administered doses to the FDA investigator, and you advised us that the revised table was submitted to the sponsor. However, this table was not a complete and accurate report, because some of the values were estimated. Moreover, the report did not identify those values as estimated. See 2. below.

2. For 10 of 22 doses (Subjects [redacted] –2 doses, [redacted] 2 doses, and [redacted]) in 1. above, the revised doses of the investigational product were estimated, rather than measured. There is no documentation that your staff performed an assay of the infusion set to determine the milliCurie activity remaining after infusion of the investigational product. The sponsor's form entitled [redacted] TRANSFER AND DOSE PREPARATION FORM [redacted] contains a section for the post-infusion assay results. There are no entries on the lines for "Residual after infusion" and "Net to patient" except for the notation "Information Not Available."

*In your letter, you said that the post-infusion survey records have not been located, and that, in the future, a checklist will be completed and signed during each procedure.*

To estimate the dose received by a subject, your staff assumed that approximately 10% of the prepared dose of the investigational product in the syringe, assayed for milliCurie activity prior to administration, remained in the infusion set after administration. Your staff justified the use of a 10% figure in making estimates by citing the North Carolina Regulations for Protection Against Radiation (North Carolina Radiation Regulations) (http://www.drp.enr.state.nc.us/RMS/RMS.htm), which provide that when doses of radioactive products occur outside these parameters, a recordable event has occurred.

*In your letter, you said that "the usual clinical practice in Nuclear Medicine operates under a standard deviation window of +/- 10% for both therapeutic and diagnostic procedures."*

The "window of +/- 10%" for a recordable event is not applicable to this situation. According to the North Carolina Regulations, a recordable event occurs when the measured milliCurie activity of the administered dosage differs from the prescribed dosage by more than 10 percent. These regulations do not refer to the difference between the assayed dose in a syringe prior to administration (which is not equal to the prescribed dose) compared to an estimate of a dose that was actually administered, and they do not concern the preparation of accurate data to assess whether a product is safe, pure, and potent. Furthermore, the use of a "window of +/- 10%" was not part of the investigational plan. This window does not preclude accurate documentation of the dosage of the investigational product received by a subject in a clinical trial.

Moreover, you did not provide any data to support your assumption that patients were administered the intended dose, less 10%, and it appears that your assumption was not supported by data obtained in the trial. In fact, when your staff performed post-infusion assays for 28 doses administered to — subjects (Subjects — –2 doses, — –2 doses, ——— –2 doses, ——— —2 doses, — –2 doses, — –2 doses, — —2 doses, — –2 doses, ——— –2 doses, — -2 doses, — –2 doses), the quantity of investigational product remaining in the infusion sets ranged from 0 to 19% of the dose assayed prior to administration.

In addition to the above items, for each dose of the investigational product, please provide a copy of the dose calibrator print-out showing the milliCurie activity in the syringe prior to administration, as well as dose calibrator print-out for the activity in the infusion set after administration.

This letter is not intended to be an all-inclusive list of deficiencies in your clinical study of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

Please notify this office in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to achieve correction may result in enforcement action without further notice. The actions could include initiation of investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

Please send your written response to:

Mary Andrich, M.D.
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA Atlanta District Office listed below.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Acting District Director
Food and Drug Administration
60 Eighth Street, NE
Atlanta, Georgia 30309

Wallace C. Nunley, Jr., M.D., Chairman
Carolinas Healthcare System Institutional Review Board
1000 Blythe Boulevard
Charlotte, North Carolina 28232